Gerontology And Geriatric Research

SCIENTIFIC LITERATURE

Research Article

Impact of Heart Rate Variability on the Risk of Neurocognitive Disorders in Older People

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ARTICLE INFO

Received Date: August 29, 2022
Accepted Date: September 14, 2022
Published Date: September 20, 2022

KEYWORDS

Neurocognitive diseases;
Atrial fibrillation; Variability;
Older adults

Citation for this article: Alexis Minouflet, Khelifa Hamouchi, Massinissa Haouchine, Béatrice Berteaux, Jean-Marie Sérot, Ingrid Gyselinck, Salif Dao, Olivier Balédent and Jadwiga Attier-Zmudka. Impact of Heart Rate Variability on the Risk of Neurocognitive Disorders in Older People. Gerontology And Geriatric Research. 2022; 4(2):132

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ABSTRACT

Introduction: Major Neurocognitive Disorders (NCD) are a major burden to society. The mechanisms involved in their development are not well understood. There is emerging evidence that variability in certain physiological parameters, may play a role in the development of NCD. In this study we focused on Atrial Fibrillation (AF), using the number of arrhythmia episodes per day as a marker of variability. The objectives were to determine whether a large number of arrhythmias per day was associated with cognitive decline and major NCD.

Methods: In the geriatric department of the general hospital of Saint-Quentin (France), we recruited 93 cognitively impaired patients aged 75 years and older. We administered a battery of tests and examinations including a comprehensive geriatric evaluation, neuropsychological testing, MRI, and a 24-hour ECG. We first compared the outcomes of patients with and without AF. We then focused on AF patients and made comparisons based on their cognitive impairment and number of arrhythmic episodes per day.

Results: The results showed no difference between AF and non-AF patients from a cognitive perspective. In contrast, among AF patients, those with more arrhythmic episodes were more likely to have low cognition and major NCD.

Discussion: More than AF itself, the number of arrhythmic episodes per day appears to influence the rate of cognitive decline and the risk of developing NCD. These results are consistent with the theory that variability in physiological parameters negatively impacts cognition.

INTRODUCTION

Major Neurocognitive Disorders (NCD) have enormous consequences for the individuals affected, their families, as well as the health care system and the economy. According to the WHO, 50 million people worldwide live with major NCD in 2020. The total number of people with major NCD is expected to reach 82 million by 2030 and 152 million by 2050. The prevalence of this disease increases exponentially with age and doubles every 5 years after age 65 [1]. In the general population, it is estimated that between 5 and 8% of people aged 60 and over have major NCD at some point [2]. Life expectancy is increasing worldwide, with a more rapid aging of the population in low- and middle-income countries, so an increase in the prevalence

of major NCD is expected, which will be associated with an explosion of costs for health services, knowing that health problems are also on the rise among family caregivers looking after relative suffering from neurocognitive disorders (stress, depression...) [3]. The total cost of neurodegenerative diseases worldwide was estimated at $818 billion in 2015 [4] and we can expect this number to increase in the future.

It is well known that aging is the main factor influencing the development of a major NCD. But this is not the only one: cardiovascular disease, heart failure, atrial fibrillation and stroke have also been identified as risk factors for cognitive deficits and major NCD [5-8]. Indeed, these diseases affecting the cardiovascular system can cause or worsen cerebral hypoperfusion, creating a cellular energy crisis leading to a cascade of events leading to the production of toxic proteins that can then be at the origin of the development of NCD [9]. In addition, midlife risk factors such as high blood pressure, familial hypercholesterolemia, overweight, and type 2 diabetes have also been associated with an increased risk of major NCD in late life [10,11]. Factors such as inflammation, obstructive sleep apnea, depression or environmental and occupational factors (tobacco, alcohol...) may also play a role in increasing the risk of developing an NCD [12-16].

Even if all the mechanisms linking these risk factors to the development of NCD are not clear, their impact is no longer in doubt. However, some studies are beginning to suggest that variability of certain physiological parameters may play a role in the development of these NCD. For example, in type 2 diabetic patients, it has been shown that those with episodes of hypoglycemia were more likely to develop a NCD [17]. Similarly, it has been suggested that high blood pressure variability may increase the risk of developing a major NCD [18]. In addition to these variations in blood pressure and glycemic levels, similar observations have been made for variations in body weight (diet/weight regain) and lipid levels [19,20]. Thus, it is possible that having variations in certain physiological parameters from a pathological state to a normal state and back on multiple occasions is one of the causes of the increased risk of cognitive decline.

There is growing evidence that Atrial Fibrillation (AF) is a risk factor for cognitive decline and major NCD independent of stroke [21-23]. Similar to blood pressure and glycemic levels seen previously, one might ask whether a high number of arrhythmia events is related to a greater risk of neurocognitive impairment. Thus, the aims of this study were: 1) to assess the association between AF and the occurrence of major NCD and 2) to investigate the impact of the number of arrhythmic episodes per day on cognition.

METHODS

Study protocol and recruitment

93 patients were recruited for this study. All patients were informed about the objectives of the study and provided informed consent to participate. Participants were explained the study protocol, including conditions for participation in all medical tests, and had a few days to make a decision before they signed written informed consent. Informative meetings were also organized for families. Even after signing the consent, the patient was allowed to stop the protocol at any time. All patients were hospitalized in the geriatric department of the General Hospital of Saint-Quentin (France). Only patients with no acute medical conditions were screened. All participants underwent the same protocol consisting of blood testing, comprehensive geriatric assessment, neuropsychological assessment, structural Magnetic Resonance Imaging (MRI), phase contrast-MRI (PC-MRI), and 24-hour Electrocardiogram (ECG). At the end of the protocol, each patient and his general practitioner were informed about the results. The inclusion criteria were as follows: age ≥75 years, male or female sex, cognitive impairment diagnosed by a physician, consent to participate in the study. The exclusion criteria were as follows: age <75 years, contraindication to MRI, history of chest or neurosurgical surgery and physical handicap. All patients who met the inclusion and exclusion criteria were included in the study in a consecutive sampling approach.

Clinical investigations

All investigations, that is, comprehensive geriatric assessment, neuropsychological assessment, blood tests, MRI, and 24-hour ECG were performed in General Hospital in Saint-Quentin, France. All results were analyzed in the hospital by the hospital staff. The comprehensive geriatric assessment was performed and interpreted by the same experienced geriatric nurse and geriatrician. The neuropsychological assessment was performed and interpreted by one of the 2 neuropsychologists involved in this study. Blood tests were done by experienced geriatric

nurses and analyzed in a laboratory by biologists. Structural MRI findings were analyzed and interpreted by the same radiologist. PC-MRI acquisitions were analyzed with a dedicated software by the main investigator, and the results were checked by the CHIMERE research team in the BioFlowImage laboratory in Amiens, France. After primary entry, all data were checked for consistency at least 3 times.

Study parameters

Clinical parameters and comprehensive geriatric assessment: A comprehensive medical history was obtained from medical records, previous interviews with patients and their families, and informative letters from general practitioners. A complete list of previous diagnoses, vascular risk factors, and current medication use for each patient was compiled and recorded in the study database. A complete clinical examination was performed at baseline. All patients showed stable hemodynamic state. There were no signs of acute or chronic heart failure, no symptoms of dehydration, no symptoms of carotid stenosis, and no bruit on carotid artery auscultation. A detailed neurological assessment revealed no abnormalities. Each patient underwent a comprehensive geriatric assessment.

Any data that could not be obtained during the visit were collected from the hospital database containing information on the population of the administrative region of Saint-Quentin. All the results were communicated to the patient's general practitioner.

Laboratory parameters: Blood tests were performed after at least 10-hour fasting.

Neuropsychological parameters: The objective neuropsychological assessment with the involvement of 2 neuropsychologists was performed. The assessment included several tests for evaluate the cognitive function:

Assessment of overall cognitive efficiency:

- MMSE (Mini-Mental State Examination) is a test extensively used in clinical and research settings to measure cognitive impairment. It includes simple questions and problems in several areas: the time and place of the test (orientation), repeating lists of words (registration), arithmetic (calculation), recall words, language use and comprehension, and basic motor skills [24].
- The MoCA (Montreal Cognitive Assessment) is a test used as a cognitive screening tool for mild cognitive impairment, it examines attention, concentration, executive function, memory, language, visuoconstructive skills, conceptual thinking, calculation and orientation [25].
- MDRS (Mattis Dementia Rating Scale) is used to assess the general cognitive status in adults with cognitive impairment. It is comprised of 5 subscale scores in the areas of: attention, initiation-perseveration, construction, conceptualization, and memory [26].

Evaluation of the memory area:

- Wechsler Adult Intelligence Scale - Digit Span task is a task that measures working memory, attention, encoding, and auditory processing [27].
- Grober-Buschke test is a verbal episodic memory test, consisting of a list of words. It examines 3 memory processes: encoding, storage, and recalling [28].
- Doors and People test is a test designed for use as a clinical and research tool. It tests visual episodic memory with recall and recognition tasks [29].

Assessment of the executive function:

- Stroop Color and Word Testis a test used to measure cognitive flexibility, resistance to interference from outside stimuli, and the ability to suppress a prepotent verbal response [30].
- Trail Making Test is a speeded test that measures sustained visual attention, visual scanning, sequencing, and cognitive flexibility[31].
- Categorical Verbal Fluency (CVF) and Literally Verbal Fluency (LVF) test is a test that evaluates the generation of semantic and phonetic information by the patient [32].
- Frontal Assessment Battery is a brief tool that can be used at the bedside or in a clinical setting to assist in discriminating between dementias with a frontal dysexecutive phenotype and dementia of the Alzheimer type [33].

Assessment of instrumental functioning:

- Oral denomination of 80 images is a test that evaluates language capacities of subjects [34].
- Token Test is a brief measure of auditory comprehension used to identify receptive language dysfunction [35].

- Brief screening scale evaluating praxis abilities evaluates the praxis abilities of an individual. It includes 3 different dimensions: verbal execution of symbolic gestures, verbal execution of action mimes (Pantomimes), and imitation of abstract gestures [36].
- BEC96 (Signoret's Battery of Cognitive Efficacy) evaluates the visuoconstructional abilities of an individual [37].
- Rey Complex Figure Test measures recall memory, visuospatial recognition, response bias, processing speed and visuoconstructional ability [38].

To compare the cognitive levels of each group of patients we calculated the cognitive level of each patient by dividing the scores of each test by the maximum score to obtain a percentage score, and then averaged all tests to obtain the cognitive level of each patient between 0 and 1.

Radiological parameters: Participants underwent conventional structural cerebral MRI protocol in which quantitative flow sequences were added to investigate the Cerebral Blood Flows (CBF) [39].

24-hour ECG: Patients underwent 24-hour ECG monitoring using a 2-channel 24-hour ambulatory tape recorder (LivaNovaSpiderview). Two-channel recording prevented possible artefact contamination in the analysis of heart rate and heart rate variability. After visual evaluation for arrhythmia and extrasystoles, the ECG data were digitized and transferred to a computer for analysis. A standard program (SORIN SyneScope) detected and calculated pathological events as well as dynamics of heart rate and heart rate variability as measured in time domain. The number of AF episodes per 24 hours was recorded.

Statistical analysis

Nominal data were expressed as numbers and percentages, while continuous data were expressed as mean and standard deviation. Comparisons were made using the χ^2 test or Fisher's exact test for categorical variables and t-test or Wilcoxon rank sum test for quantitative variables. A linear regression was used to evaluate the relationship between several variables. An alfa value of 0.05 was assumed as statistically significant. Statistical analyses were performed using R Core Team (2021). The handling of missing values was parameter-dependent. No patient was excluded from the study even if he presented missing values.

Ethical considerations

The study protocol was approved by an independent Regional Ethical Review Board in Amiens (CPP: 2015/6). The French Data Protection Authority (CNIL: 150075B-31) gave its consent for the data to be entered. Study was registered in clinicaltrials.gov (NCT02578303).

All procedures were performed according to the Declaration of Helsinki. All participants were informed about study objectives and procedures and provided their written informed consent to participation. The consent was signed by the patients who were able to understand the main terms of the protocol; in the case of doubt in inability, the consent was signed by a family member.

Medical consultations

The results of all procedures (comprehensive geriatric assessment, blood tests, neuropsychological assessment, and MRI) were forwarded to general practitioners of the participants. On study completion, all participants were invited to a consultation with the main investigator. If a previously unknown pathology was found, the patient was referred to a specialist department or clinic for further consultations.

RESULTS

The study population consisted of 93 participants, of whom 36 presented at all visits and completed all tests. For comprehensive geriatric assessment, 58 fully completed questionnaires were returned. Any missing data were related to memory disorders of patients and incomplete medical records. For blood tests, there were no missing data. The neuropsychological assessment was performed in 98 participants, and the results were validated by a neuropsychologist. The data for particular tasks were missing either due to refusal of patients to undergo a task or due to fatigue. For MRI, the results of 89 exams were considered valid. The missing MRI values were due to refusal to undergo the exam, behavioral disorders of patients, or technical problems (gating).

The average age of the study population was 83.69 years (±5.19 years), the majority were women (77%).

First, we compared the results between two groups according to the diagnosis or not of AF: an "AF+" group of 15 patients

with AF and an "AF-" group of 78 patients without AF. We did not observe any significant difference between these groups. These results are presented in Table 1.

Table 1: Demographics of our population and comparison between AF+ and AF-

Variable	Overall, N=93[1]	AF-, N=78[1]	AF+, N=15[1]	p-value[2]
Age	83.69 (±5.19)	83.47 (±5.10)	84.80 (±5.68)	0.27
Sex				0.18
Men	21 (23%)	20 (26%)	1 (7%)	
Women	72 (77%)	58 (74%)	14 (93%)	
Major NCD				0.61
Yes	49 (53%)	42 (54%)	7 (47%)	
No	44 (47%)	36 (46%)	8 (53%)	
Average cognitive level	0.69 (±0.11)	0.69 (±0.12)	0.68 (±0.09)	0.56
CBF	545.03 (±170.81)	529.85 (±146.45)	636.09 (±267.75)	0.33

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

Abbreviations: AF: Atrial Fibrillation; NCD: Neurocognitive Disorder; CBF: Cerebral Blood Flow.

Mean (standard deviation) is shown for quantitative data and number (percentage) is shown for qualitative data. Comparison between AF+ and AF- by Wilcoxon rank sum test, Fisher's exact test and Pearson's Chi-squared test. p-value < 0.05 shows a significant difference.

Table 2: Comparison of patients with and without NCD in the AF+ group.

Variable	Overall, N=15[1]	NCD-, N=8[1]	NCD+, N=7[1]	p-value[2]
Age	84.80 (±5.68)	83.25 (±6.84)	86.57 (±3.74)	0.49
Sex				>0.99
Men	1 (7%)	1 (12%)	0 (0%)	
Women	14 (93%)	7 (88%)	7 (100%)	
Arrhythmic episodes	39.73 (±47.42)	10.25 (±15.23)	73.43 (±49.94)	**<0.01**

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Fisher's exact test

Abbreviations: NCD: Neurocognitive Disorder. Mean (standard deviation) is shown for quantitative data and number (percentage) is shown for qualitative data. Comparison between NCD+ and NCD- by Wilcoxon rank sum test and Fisher's exact test. p-value < 0.05 shows a significant difference.

Next, we focused on patients with AF and divided them into 2 groups based on whether they had a diagnosis of major NCD (NCD+) or not (NCD-). Patients in the NCD+ group presented more AF episodes per 24 hours (73.43 ± 49.94) than those in the NCD-group (10.25 ±15.23). Indeed, patients without major cognitive problems have less than 50 episodes per 24 hours, whereas the majority of patients with a major NCD (71%) have more than 50 episodes per 24 hours. These results are correlated with the cognitive level: the group of patients with less than 50 AF episodes per 24 hours has a better average cognitive level. These results are described in Tables 2 and 3. Regarding CBF, we did not observe any significant difference between the groups.

Table 3: Comparison of patients with more or less than 50 arrhythmic episodes per day in the AF group.

Variable	Overall, N=15[1]	Over 50 episodes, N=5[1]	Under 50 episodes, N=10[1]	p-value[2]
Age	84.80 (±5.68)	86.40 (±3.58)	84.00 (±6.51)	0.76
Sex				>0.99
Men	1 (67%)	0 (0%)	1 (10%)	
Women	14 (93%)	5 (100%)	9 (90%)	
Major NCD				**<0.01**
Yes	7 (47%)	5 (100%)	2 (20%)	
No	8 (53%)	0 (0%)	8 (80%)	
Average cognitive level	0.68 (±0.09)	0.60 (±0.05)	0.73 (±0.06)	**<0.01**

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Fisher's exact test

Abbreviations: NCD: Neurocognitive Disorder. Mean (standard deviation) is shown for quantitative data and number (percentage) is shown for qualitative data. Comparison by Wilcoxon rank sum test and Fisher's exact test. p-value < 0.05 shows a significant difference.

DISCUSSION

Firstly, our population consisted exclusively of patients who were hospitalized in the geriatric department. The patients recruited were in a condition that allowed them to participate in the study (no acute medical condition). The reasons for hospitalization were not critical (most often for falls).

In this study of 93 patients aged 75 years and older, 15 had AF. In the general population over 60 years of age, the prevalence of AF is estimated at 1% [40]. With 15% of our population, we are well beyond this figure. This is certainly due to the fact that our patients are older and AF increases with age and that this is an inpatient population and therefore less healthy than the general population of the same age so it is not surprising to find more subjects with AF. Thus, in this population, we observed no significant difference between the AF- and AF+ groups. These results are in contrast to what is observed in the literature regarding the association between AF and major

neurocognitive impairment although the populations for which this association was described were younger than ours [21-23]. This contrast may be due to our small number of patients with AF.

Focusing on our 15 patients with AF, we observed that patients with major NCD had more AF episodes per 24h than patients without major NCD. In addition, all patients without major NCD had fewer than 50 episodes of AF per 24h, whereas 5 of the 7 patients with major NCD had more than 50 episodes per 24h. We observed an association between the number of arrhythmic episodes per day and cognitive level since subjects with less than 50 AF episodes per 24h demonstrated a significantly better cognitive level than those with more than 50 episodes per 24h. This last result must be qualified by the fact that in the "under 50 AF per 24h" group there is a majority of subjects with a major NCD in comparison with the "over 50 AF per 24h" group, so a lower cognitive level appears logical. In view of the small number of subjects, it is impossible to determine whether the large number of AF per 24h is responsible for the development of major NCD and therefore a logically lower cognitive level or whether the results are biased by an unequal distribution of patients in the two groups.

Finally, regarding cerebral perfusion, we did not observe a significant difference in CBF. Indeed, cerebral hypoperfusion could explain the association between AF and major NCD by 2 potential mechanisms: 1) the beat-to-beat variability of AF leading to frequent episodes of cerebral hypoperfusion [41]; and 2) the global reduction of cardiac output in AF due to the absence of atrioventricular synchronization [42]. Thus, one would have expected to observe a lower CBF in patients with a significant number of AF episodes per 24h illustrating this cerebral hypoperfusion. Because of the irregular nature of the cardiac rhythm in AF, it is possible that beat-to-beat variability in cerebral perfusion may coexist during AF compared with regular sinus rhythm. For this, our method of assessing mean cerebral perfusion via CBF may not be the correct one. Perhaps a CBF measurement should have been performed for each cardiac cycle and thus the occurrence of cerebral hypoperfusion episodes could have been observed more precisely. One study evaluated the effect of irregular pacing in AF on proximal and distal cerebral flow using two in vitro models. Although mean flow in the vessels was similar in AF and sinus rhythm, they found greater flow variability in AF, particularly in the distal circulation. In addition, more than 300 episodes of hypoperfusion were observed per 5000 cardiac cycles evaluated. The results of this in vitro model suggest that cerebral hypoperfusion may occur independently of cardiac output in patients with AF because of beat-to-beat variability in cerebral perfusion [41]. Although cerebral hypoperfusion may be present, the mechanisms by which it exerts its effect on cognition remain to be elucidated. Furthermore, because of the contradictory nature of the results, mechanisms unrelated to CBF may play a more important role in affecting cognition.

CONCLUSION

This study tends to support the hypothesis that variability in some physiological parameters within major NCD risk factors may play an important role in the prevalence of cognitive impairment. These results may allow for more accurate detection of risk factors for neurocognitive disorders. Here with taking the example of atrial fibrillation, we did not observe a difference by simply discriminating according to whether or not they had AF but we did observe differences by focusing on the number of AF episodes per 24 hours. However, given the small number of patients with AF in this study, this would require confirmation of these results by a study with more subjects with AF.

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